



Tuberculosis evolution and climate change: How much work is ahead?

Dear Sir,

In the *Annus Domini* (A.D.) or Common Era, there have been some changes in climate conditions worldwide. It has been recognized that a warm Roman period lasted from around 250 BCE through 400 A.D., just a few decades before the fall of the Roman Empire. In the mid of the first millennium (535–536 A.D.), probably caused by volcanic dust, an impressive period of sudden freezing occurred in several parts of the world. This aspect has been associated with the failure of harvest and catastrophic famine of the early Middle Ages. In the late Middle Ages, a warm period has been noted between 900 A.D. and 1300 A.D., indeed. This period was quite rainy and calamitous in Europe, while extremely arid in North America with numerous wildfires. It may have been a causative factor in the landscape alterations of the Great Plains of North America. The Great Famine of 1315–17 A.D. in Europe has also been associated with a climate change with some freezing up to glaciation periods, particularly in northern Europe, noted between 1250 and 1550 in Europe. Years with low or extreme temperatures have been recorded between 1460 and 1830 for about four centuries. In particular, the year 1816 was a time considered without a summer, probably caused by intense volcanic activity. Since 1850, it seems relevant that there is a retreat of glaciers, which may have dreadful effects for future generations. Currently, scientific papers and communication media such as the press and broadcasting are inundating the public opinion with data and/or information focusing on the uncertain climatic conditions of the 22nd century.

It is quite well known that the burden of malaria infection in the setting of climate conditions. *Plasmodium falciparum* is correlated with regional changes of temperature (Wilkinson and Grover, 1996). Malaria infection is an important cause of low birth weight and morbidity when it is associated with placental infection (Kassam et al., 2006). In Rwanda, infection with *P. falciparum* spoke in places initially devoid of this infection. It occurred in higher altitudes after a period of warm weather in the 1980's. A similar situation happened in Italy in the last decades of the 19th century, which promoted the bonification of several areas before the 2nd world war. Computer simulation with aggregated models has predicted a temperature increase caused by global warming of about 15% by the year 2100, especially for populations living in a zone with high potential malaria infection (Wilkinson and Grover, 1996). Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is one of the top 10 causes of death worldwide and increasing and remains one of the leading causes of global morbidity and mortality. Currently, TB is considered a health security threat for several countries. It is impressive the emergence and spread of multi-drug resistant (MDR) TB. Now and in the nearest future, MDR-TB is a big challenge for healthcare policymakers. One of the health targets of "Sustainable Development Goals" is to end the TB epidemic by 2030, which may not be attainable in consideration of climate change. In particular, the focus on the diffusion of extensive drug-resistant (XDR) TB will be key (Yang et al.,

2016). XDR TB has been defined as resistance to both first-line drugs, rifampicin, and isoniazid, in combination with at least two of the 2nd line drugs, including a quinolone plus one of the injectable drugs (amikacin, kanamycin or capreomycin). XDR TB has now been reported from about sixty countries with South Africa reporting one of the highest incidences of XDR TB worldwide (Abayomi and Cowan, 2014). This situation is related to the HIV epidemic, which is thought to drive the healthcare emergency. Africa is a vast continent and is especially vulnerable to climate change, generally speaking, because of its high cargo of diseases, scarcity of fundamental (e.g., nutritional) resources, historical socioeconomic inequality, and abnormal density of population distribution with several countries having masses of people in poverty. In Africa, significant patterns of gradual warming and shifts towards more variable and intense rainfall distribution have been observed in a half century. Climate modeling computing and simulation for some African countries point to some dramatic situations. Some states or eastern regions are becoming wetter, while the western and interior areas are becoming drier. It has been estimated that by 2100 global warming is projected to reach around 3–4 °C along the South African coast, and 6–7 °C in the central regions. South Africa, as well as other African countries, may experience a worsening of the HIV-TB combined epidemics, which threatens to exacerbate ecological instability amid climate change with migratory fluxes. Apart of Africa, researchers have investigated the influence of seasonal variations on the transmission dynamics of infectious diseases during the last couple of decades. Annual difference in TB incidence has been described in many countries, such as India, the United States, the Russian Federation, Hong Kong SAR, Taiwan, and China mainland (Atun et al., 2005; Behera and Sharma, 2011; Hu, 2012; Leung et al., 2005; Li et al., 2013; Liao et al., 2012; Liu et al., 2010; Willis et al., 2012). TB will play a significant role for a couple of decades, probably until 2050. The actual incidence of MDR and XDR TB in several countries remains largely unknown due to the lack of drug susceptibility tests in the vast majority of centers. States of the former Soviet Union have seen some of the highest proportion of MDR rates and some of the worst resistance patterns. If in addition to global warming, public-health systems will collapse without affordable privacy sectors and there will not be enough national programs for case detection and treatment, the situation will worsen earlier. In our opinion, policymakers should address efficiently and effectively the poor laboratory support for drug susceptibility testing and having little political commitment to avoid jeopardizing the microbiology scenery that threatens the future of humanity. The introduction of new molecular biology techniques and the pledge of several countries in providing low-cost devices to low-income countries is a terrific step for stopping inequality in the world. In particular, the healthcare system should strengthen and address the needs of the most vulnerable populations, i.e., the children (Kiang et al., 2013; Yacoub et al., 2011). Programs, such as "Stop TB", will be successful if critical interventions in the setting of social and economic

development will provide an important platform worldwide.

In conclusion, we have significant challenges ahead that we cannot minimize. Climate change will not affect people equally but will amplify already immense resource and wealth disparities within and between countries. Low-income countries remain the most vulnerable ones (Kiang et al., 2013) and this aspect has been raised for vaccination protocols as well (Leung et al., 2018). Although our knowledge of sepsis and infection, as well as the interaction between host and pathogen, are better understood now than ever (Sergi et al., 2017), the changes in the environment can render our efforts for treatments and vaccinations elusive. A call for joint efforts, multicultural symposia, and biotechnology workshops needs to be put in place to increase our knowledge of current microbiological research and to evaluate the TB challenges ahead correctly (Sergi, 2018). The refining of diagnostic methods should be supported by the acquisition of knowledge derived by the application of new machines, e.g., Next Generation Sequencing. The correct use of this molecular biology platforms will be the basis for a restructuration of health care policy for the 22nd century.

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Consolato Sergi^{a,*}, Nicola Serra^b, Claudia Colombo^c,

Ayansina Ayanlade^d, Paola Di Carlo^c

^a Department of Laboratory Medicine and Pathology, Stollery Children's Hospital, University of Alberta, Edmonton, Canada

^b Department of Pediatrics, University Federico II of Naples, Italy

^c Department of Sciences for Health Promotion and Mother and Child Care, University of Palermo, Palermo, Italy

^d Department of Geography, Obafemi Awolowo University, Nigeria

E-mail address: sergi@ualberta.ca (C. Sergi).

* Corresponding author at: Department of Laboratory Medicine and Pathology, University of Alberta, 8440 112 St, Edmonton, AB, Canada.